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February 26, 1998

BOX PCT

Assistant Commissioner for Patents
Washington, D.C. 20231

Attorney Docket No. 3103/44139

Re: Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing Under 35 U.S.C. §371

International Application No.: PCT/IL96/00089
International Filing Date: August 29, 1996

Priority date claimed: August 31, 1995
Priority application number: 115113

Inventorship: Eliezer RACHAMAN, Eliahu HELDMAN, Rachel ADANI, and Gabriel AMITAI

Title: PYRIDINIUM DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Enclosed herewith for entering the national stage in the United States is the above-referenced international application.

APPLICANT WISHES THAT THE ANNEXES TO THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT REPLACE THE APPROPRIATE PAGES OF THE CLAIMS AS FILED.

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.

2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.

3. [X] This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. §371(c)(2))

   a. __X__ is transmitted herewith (required only if not transmitted by the International Bureau).

   b. ____ has been transmitted by the International Bureau. A copy of Form PCT/IB/308 is attached hereto.

   c. ____ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [ ] A translation of the International Application into English (35 U.S.C. §371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))

   a. ____ are transmitted herewith (required only if not transmitted by the International Bureau)

   b. ____ have been transmitted by the International Bureau

   c. ____ have not been made; however, the time limit for making such amendments has NOT expired

   d. ____ have not been made and will not be made

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)) is:

   [ ] Attached in the regular manner.
   [X] NOT included, but deferred under P.L. 97-247.

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5))

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [ ] An Assignment of the invention in favor of the following organization is enclosed for recordation. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A **FIRST** Preliminary Amendment.

    [ ] A **SECOND** or **SUBSEQUENT** Preliminary Amendment.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [ ] Other items of information:

    [ ] Form PCT/RO/101 Request (in English/in French)

    [ ] Small Entity Declaration Under 37 C.F.R. 1.27

    [ ] ____ Sheets of Formal Drawings
    [ ] ____ Sheets of Informal Drawings

    [ ] The content of the paper and computer readable copy of the attached Sequence Listing, submitted in accordance with 37 CFR §1.821(c) and (e), respectively, are the same.

    [X] Kindly appoint as associate attorneys (if not already a principal attorney) or agents:

    Martin Fleit, Reg. No. 16,900; Herbert I. Cantor, Reg. No. 24,392; James F. McKeown, Reg. No. 25,406; Donald D. Evenson, Reg. No. 26,160; Joseph D. Evans, Reg. No. 26,269; Gary R. Edwards, Reg. No. 31,824; Jeffrey D. Sanok, Reg. No. 32,169; Richard R. Diefendorf, Reg. No. 32,390; and Paul A. Schnose, Reg. No. 39,361

[X] The total amount due for the filing fee in this case is:

[ ] Based on Small Entity Status

Total Number of Claims: 14
Total Independent Claims: 2

Basic filing fee, $930/$465.	$ 930.00
Independent Claims above 3, $82/$41 ea.. . . .	$ 0
Total claims in excess of 20, $22/$11 ea.. . .	$ 0
Multiple dependency penalty, $270/$135	$ 0
Declaration surcharge, $130/65	$ 0
English translation surcharge, $130	$ 0
TOTAL FILING FEE DUE	$ 930.00

Please forward all communications regarding this application to the undersigned at the letterhead address.

Respectfully submitted,

Herbert I. Cantor
Reg. No. 24,392

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY FEES WHICH MAY BE REQUIRED OR CREDIT ANY OVERPAYMENT TO DEPOSIT ACCOUNT NO. 05-1323. THIS FORM IS FILED IN DUPLICATE.

THIS IS A GENERAL AUTHORIZATION EXCLUDING ONLY PAYMENT OF THE ISSUE FEE.

HIC/jaf

Attorney Docket: 3103/44139
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: ELIEZER RACHAMANN ET AL.

PCT No.: PCT/IL96/00089

INT'L FILING DATE: AUGUST 29, 1996

Serial No.: NOT YET ASSIGNED Group Art Unit:

Filed: HEREWITH Examiner:

Title: PYRIDINIUM DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please enter the following amendments to the claims and abstract prior to the examination of the application.

IN THE CLAIMS:

Please amend the claims as follows:

Claim 3, line 1, change "claims 1 or 2" to --claim 1--.

--8.(Amended)A method [pharmaceutical composition of any of claims 5 to 7] for the treatment of, and for the alleviation of symptoms of CNS diseases associated with cholinergic disorders and for the alleviation of side-effects induced by antimuscarinic tricyclic antidepressants which [comprise] comprises administering an effective [quantity] amount of a [compound claimed in any of claims 1 to 4 or as defined in claim 5] composition as defined in claim 5.--

Claim 9, line 1, change "anyy of claims 5 to 7" to --claim 5--.

--10.(Amended) A method [composition according to any of claims 5 to 7] for the treatment of, and alleviation of symptoms of peripheral cholinergic disorders, glaucoma, myasthenia gravis,

treatment of urine bladder dome ([neurgenic] neurogenic urine bladder) and for the pretreatment of organophosphorus intoxication in combination with known antimuscarinic, antinicotinic drugs and antagonists of the excitatory amino acid receptors such as glutamate receptor, comprising an effective [quantity] amount of a [compound claimed in any of claims 1 to 4 or as defined in claim 5] composition as defined in claim 5.--

Claim 11, line 1, change "any of claims 5 to 7" to --claim 5--.

--14. (Amended) Pharmaceutical combinations of the 3-positioned substituted pyridinium compounds as defined in claim 5 [and compositions containing them as defined in claim 10] together with nicotinic and/or muscarinic and/or glutamate antagonists which confer higher efficacy than each one of them by itself, for the treatment of hypercholinergic impairments such as intoxication caused by reversible and irreversible cholinesterase inhibitors that are chemical warfare nerve agents.--

IN THE ABSTRACT:

Please substitute the new Abstract of the Disclosure attached hereto on a separate page for the original Abstract presently in the application.

REMARKS

Entry of the amendments to the claims and abstract before examination of the application is respectfully requested. These

claims have been amended to remove multiple dependencies thereof and to place the application in better form for U.S. practice.

If there are any questions regarding this Preliminary Amendment or this application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

It is respectfully requested that, if necessary to effect a timely response, this paper be considered as a Petition for an Extension of Time sufficient to effect a timely response and shortages in other fees, be charged, or any overpayment in fees be credited, to the Account of Evenson, McKeown, Edwards & Lenahan, P.L.L.C., Deposit Account No. 05-1323 (Docket #3103/44139).

Respectfully submitted,

February 26, 1998

Herbert I. Cantor
Registration No. 24,392

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105 Rec'd PCT/PTO 26 FEB 1998
PCT/IL96/00089
09/029543

PYRIDINIUM DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Background of the Invention

Cholinergic deficiency in the central nervous system is associated with cognitive impairment (1,2,3). In pathological conditions such as Alzheimer's disease (AD) cholinergic deficiency has been consistently observed in discrete brain regions such as the nucleus basalis of Minert and the cerebral cortex and the hypocampus (4,5). Therefore, a rational approach for the treatment of such cognitive impairments would be to elevate the level of acetylcholine in brain. Cholinesterase (ChE) inhibitors such as physostigmine (PHY) and tacrine (THA) has been clinically examined as potential treatment for AD. PHY displayed fairly consistent mild positive benefits (6). Yet, its short half-life and relatively high acute toxicity limits its clinical use. THA, a long-acting reversible ChE inhibitor, is the only drug approved so far by the FDA for the treatment of AD patients (7). However, its hepatotoxicity and peripheral side effects on the GI system such as nausea and vomiting combined with its moderate efficacy only at high doses constitute its major disadvantages (8). Pyridostigmine (PYR) is a reversible ChE inhibitor which is less toxic than PHY and has a longer duration of action than PHY. PYR serves as an effective drug for the treatment of myasthenia gravis (MG) (9). MG is an autoimmune disease in which the functional nicotinic cholinergic receptor is diminished and it can be treated by prolonging the presence of acetylcholine in the synapse with AChE inhibitors such as PYR (9). PYR is also used for the pretreatment of humans against poisoning by organophosphorus insecticides and nerve agents (6). If PYR were more permeable through the blood-brain barrier (BBB) it could have been used also for the treatment of central cholinergic deficiency. However, its quaternary positively charged pyridinium nitrogen limits its permeability into the CNS and confines its use only as a peripheral cholinomimetic drug (6). Earlier efforts were made to develop tertiary

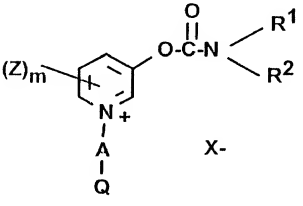
analogues of PYR but they displayed lower efficacy than PYR as AChE inhibitors (10). The development of PYR derivatives that could cross the BBB, will have longer duration of action and will be less toxic than the existing AChE inhibitors PHY, THA and PYR, will provide a new series of cholinomimetics with improved efficacy and safety.

Summary of the Invention

The molecular design of the new ChE inhibitors which are related to the structure of PYR is based on the attachment of aliphatic chains of various lengths (vide infra) to the quaternary pyridinium nitrogen of PYR. Such carbohydryl chains conjugated to the PYR structure introduce lipophilicity to the resulting new molecule as was shown by the increased distribution coefficient in n-octanol as compared to water (vide infra). According to the three dimensional structure of AChE it was shown that the active site serine residue at position 200 (Torpedo AChE) is located in a 20Å deep narrow gorge lined by many aromatic residues (11). The aromatic residues Tyr337 and Trp84 which reside inside the gorge interact with positively charged quaternary nitrogen of substrates (e.g. acetylcholine) or inhibitors (e.g. edrophonium and PYR) (12). Based on the AChE protein structure and topology, we postulated that a long flexible carbohydryl chain coupled to PYR basic structure will not affect significantly the inhibition potency of the carbamate. On the other hand, due to their increased lipophilicity these compounds would display longer elimination kinetics from blood compared to that obtained for PYR, PHY and other known carbamates (vide infra). Sufficiently long carbohydryl (aliphatic, alicyclic or mixed alipahatic/alicyclic) chains could also serve as spacers or anchors for the attachment of functional groups that may further increase the bioavailability in the CNS and improve the pharmacokinetic profile of the molecule. These functional groups constitute specific carrier recognition factors for various transport mechanisms through biological barriers such as: blood-brain barrier (BBB), cell membranes and kidney tubuli. As a demonstration of

this novel concept we have chosen certain sugar moieties recognized by the glucose transporter. In addition , covalent attachment of lipophilic PYR-derivatives to biodegradable polysacharides via carbohydryl spacers may be used as precursers for sustained release of AChE inhibitors - and thus to further increase their duration of action.

The invention relates to 3-position substituted pyridinium derivative of the general formula



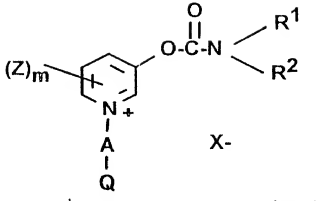
where R^1 is -H, lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

R^2 is lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

A is an alkylene, alkenylene or an alkynylene group spacer and

Z designates dialkylcarbamoyl or lower alkyl and m is zero or 1,

Q is a transporter recognition moiety adapted to enhance the transport of congeners via biological membranes, which Q entity can optionally be substituted or coupled to a physiologically active acceptable moiety, and where X^- is an anion, and to a pharmaceutical composition containing an effective quantity of compound of the formula:



where R^1 is -H, lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

R^2 is lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

A is an alkylene, alkenylene or an alkynylene group spacer and

Z designates dialkylcarbamoyl or lower alkyl and m is zero or 1.

Q is -H or a transporter recognition moiety adapted to enhance the transport of congeners via biological membranes, which Q entity can optionally be substituted or coupled to a physiologically active acceptable moiety, and where X^- is an anion.

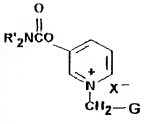
The compounds which are included in this invention are divided into two groups described by the general structural formula in figure 1: compounds of **Group A,** are N-carbohydryl substituted PYR derivatives containing moieties which increase lipophilicity. These moieties include aliphatic chains $(CH_2)_n$ with various lengths of e.g. n= 2- 24 and alicyclic or combined aliphatic and alicyclic hydrocarbon chain. **Group B,** which is described in figure 1, includes compounds which contain PYR as their basic structure and the N-substituted hydrocarbyl chain serves as a spacer arm for the attachment of functional moieties, such as sugar residues, which are recognized by various receptors and membrane transporters.

The PYR-derivatives presented in this invention can be used as a therapeutic mixture together with either known muscarinic and nicotinic agonists for hypocholinergic related impairments or with known muscarinic and nicotinic

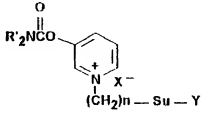
antagonists for hypercholinergic impairments, at doses which are lower than those employed for each of the drugs separately. Thus, a synergistic effect is expected for such mixtures.

Figure 1.

group A



group B



R' = alkyl or aryl residue

X^- = anionic residue

Su = a sugar residue

Y = phosphoryl or phosphatidyl residue

G is:

$R_a = (CH_2)_nCH_3$,

$R_b = (CH_2)_nAr$,

$R_c = (CH_2)_n$— cyclohexyl or

R_d = aryl- alkyl- alicyclic

n = 1 - 23

Alkylations on the 3-carbamoyl pyridine to obtain members of group A are carried out in similar methods to those described for **2** $_{a-e}$ in the chemical synthesis section (scheme 1). The members of group B include also their corresponding precursors which include suitable acetylated or benzylated glycosyl residues as well as inositol derivatives (13). The incorporation of the sugar moiety is achieved, through condensation of the sugar derivative either by its anomeric position as already desribed (see experimental section) or through one of its hydroxyl groups, which is substituted by a suitable leaving group. All the synthetic procedures of the new compounds can be scaled-up using straightforward processes.

The various sugar moieties which could be attached to the molecule via the hydrocarbon chain are:

1. Aldoses which include Aldohexoses: e.g., glucose, mannose, galactose, aldopentoses, aldotetroses and glyceroses and their corresponding aldonic and uronic acids.
2. Ketoses which include ketohexoses (e.g. fructose, sorbose), pentoketoses.
3. 6-deoxy hexoses e.g. fucose and mannose.
4. Alditols which includes manitol and ducitol (C6), ribitol (C5), erythritol (C4), and glycerol (C3).
5. Cyclohexitols (e.g., inositol and myoinositol).
6. Ascorbic acid and its derivatives (e.g. dihydro ascorbate).
7. Disaccharides (e.g., lactose, maltose and sucrose).
8. Oligesaccharides which contain either sialic acid or in the absence of sialic acid.
9. Amino sugars (e.g. glucoseamine, N-acetylglucoseamine).
10. Phosphorylated sugars (e.g. phosphatidylinositol).
11. Polysocharides (e.g. cellulose, amylose) used mainly for the sustained release of the drugs either by covalent coupling or by coating.

Chemical Synthesis

1. General procedure for the preparation of N-Alkyl-3-dimethylcarbamoyl pyridinium bromide (Group A, figure 1).

0.01M of 3-dimethyl carbamoyl pyridine was mixed with 0.015M of the corresponding alkyl bromide in acetonitrile (50cc). Initially an emulsion was obtained particularly in the case of higher alkyl halides. Upon heating the reaction mixture at 80°c. for about 16 hours; the solution gradually became homogeneous . The work-up included a purification by a silica column chromatography. Elution was carried out with ethylacetate followed by gradient

mixtures of chloroform- methanol. All six carbamates of type 2 were obtained as an oily product (see scheme 1).

n.m.r. data of **2a, b, c, d, e:**

2a:

^{1}H-nmr($CDCl_3$): 0.95(t, CH_3); 1.41(m ,$C\underline{H}_2CH_3$);

1.99(m,$C\underline{H}_2CH_2N^+$) 3.03, 3.16[2s,$N(CH_3)_2$]; 4.93(t,CH_2N^+);

8.16(m,Hγ); 8.29 (d, Hδ); 9.2 (s, Hα); 9.34(d, Hβ)ppm.

MS (FAB): m/e 223 (M^+).

2b:

^{1}H-nmr($CDCl_3$): 0.83(t, CH_3); 1.30(m, $2CH_2$); 1.32(m, $C\underline{H}_2CH_3$);

2.08(m, $C\underline{H}_2CH_2N^+$); 3.02, 3.15[2s, $N(CH_3)_2$];5.02(t, CH_2N^+);

8.25(m. Hγ);8.38(d,Hδ); 9.4(s, Hα); 9.54(d,Hβ)ppm.

MS (FAB): m/e 251 (M^+).

2c:

^{1}H-nmr ($CDCl_3$): 0.83(t,CH_3); 1.22(m, $4CH_2$); 1.30(m, $C\underline{H}_2CH_3$);

2.03(m,$C\underline{H}_2CH_2N^+$), 3.03, 3.15[2s, $N(CH_3)_2$];5.0(t,CH_2N^+); 8.18(m,Hγ);

8.37(d,Hδ) 9.28(s, Hα); 9.42(d,Hβ)ppm.

MS (FAB): m/e 279 (M^+).

2d:

^{1}H-nmr ($CDCl_3$): 0.85(t, CH_3);1.22[m,6(CH_2)];1.32(m, $C\underline{H}_2CH_3$) 2.03(m,

$C\underline{H}_2CH_2N^+$);3.03,3.17[2s, $N(CH_3)_2$];5.0(t,CH_2N^+); 8.15(dd, Hγ),

8.32 (d, Hδ) ; 9.30 (s,Hα);9.46(d,Hβ)ppm.

MS (FAB): m/e 307 (M^+).

2e:

^{1}H-nmr ($CDCl_3$); 0.87(t, CH_3); 1.23(s,8 CH_2); 1.35(m,$C\underline{H}_2CH_3$)

2.02(m, $C\underline{H}_2CH_2N^+$); 3.05, 3.18[2s, $N(CH_3)_2$];5.03(t, CH_2N^+);

8.22(m, Hγ); 8.39(d, Hδ):9.38(s, Hα); 9.51(d, Hβ)ppm.

MS (FAB): m/e 335 (M^+).

2. Preparation of Glycoside-Alkanoyl "Extended Arm" Conjugate (Group B, figure 1)

2.1 Glycosidation: (Compound 5, scheme 2)

A stirred solution of 0.08M 1,8-octanediol in 3:2 (v/v) nitromethane-benzene (90 ml) was boiled until 30ml of the solvent mixture had distilled off, to ensure complete dehydration and then cooled to room temperature. Mercuric cyanide (0.012M) and 2,3,4,6-tetra-o-acetyl- α-D-glucopyranosyl bromide (0.02M) were added, and the reaction mixture was heated at reflux for 2 hours and afterwards for 72 hours at room temperature. The reaction mixture was diluted with benzene (30cc), and washed successively with a cold, saturated aqueous solution of sodium hydrogencarbonate and water, then dried with anhydrous sodium sulfate, and finally concentrated in vacuo.

The crude product 5 (scheme 2) was purified on a silica column and eluted with a mixture of dichloromethane-ethylacetate.

^{1}H-n.m.r($CDCl_3$): 1.30 (m,3CH_2);1.57(m, 3CH_2); 2.02 (s,OAc); 2.037 (s,OAc);2.04 (s,OAc);2.08 (s,CH_2OAc);3.48 [m,H_a($CH_2OGlu.$)]; 3.63(t,CH_2OH);3.7(m,H-5);3.88 [m,H_b($CH_2OGlu.$)]; 4.15(dd, H-6_a); 4.28(dd, H-6_b); 4.48 (d,Hβ);4.99 (dd, H-2); 5.1(t, H-4); 5.21(t, H-3)ppm.

2.2 Triflylation: (Compound 6, scheme 2)

The glycoside 5 (1.5gr) obtained by the procedure described above, was triflylated in chloroform (20ml) by the addition of 2,6-lutidine (1.8cc) and triflic anhydride (1gr). The reaction mixture was stirred at room temperature for 20 hours. Afterwards, the solvent was concentrated in vacuo. The residue was taken up in ether (30cc) and separated from the triflic acid salt. The organic phase was washed with cold water, dried, and concentrated again in vacuo to give a crude product 6 (scheme 2).

2.3 Quaternization:(Compound 7, scheme 2)

A solution of 3-dimethyl carbamoyl pyridine 1 (1.6gr) and cpd. 6 (1.6gr) in acetonitrile (20cc) was stirred at 80°C for 3 hours, and for additional 20 hours at room temperature. The reaction mixture was concentrated in vacuo and purified on a silica column. Elution of the product 7 was carried out with a mixture of chloroform, methanol (4:1).

2.4 Replacement of the anion: (Compound 8a, scheme 2)

Replacement of the triflate anion with Cl^- was achieved by using an anion exchange resin (AG 1-X8, chloride-form) in methanolic solution.

^{1}H-n.m.r. ($CDCl_3$): 1.32(bs, $4CH_2$); 1.48(bs, CH_2CH_2O); 1.99, 2.02, 2.04, 2.08(4s,4-OAc); 3.05,3.17[2s,$N(CH_3)_2$];3.42, 3.65 and 3.85 (3m, $H_{a'}$,$H_{b'}$,,CH_2O-glu); 4.03(t,H-5); 4.12(dd, $H6_a$) ;4.25(dd, H-6_b); 4.48(d,Hβ); 4.94(m, H-2&CH_2N^+); 5.07(t,H-4);5.20(t,H-3); 8.16(m, Hγ); 8.33 (d, Hδ); 9.26(s,H-Arα); 9.40(d, H-Arβ)ppm.

MS (FAB) : m/e 625 (M^+).

2.5 Saponification: (Compound 8b, scheme 2)

Water (1ml) was added to a solution of 8 (250 mg) in methanol (30cc) and few drops of triethylamine were added to adjust the pH to 11. After 20 hours at room temperature the reaction mixture was neutralized with an acidic cation exchange resin (Dowex 50 H^+).

A crude saponified product 9 was obtained by purification on a small silica column, and elution with methanol. MS (FAB): m/e 458 (M^++1).

3. N-Alkyl- 3-Hydroxy-Pyridinium halides. (scheme 3, 9 a,b,c,d,e,f)

All the 6 members of compound 9 (see scheme 3),were synthesized and characterized in a similar manner to that which was described for 2 a,b,c,d,e derivatives.

9a:

^{1}H-nmr($D_2$0): 4.37(s,N^+-CH_3); 7.92(m, H-γ); 7.98(d,H-δ); 8.36(d,H-β); 8.39(s,H-α).

9b:

^{1}H-nmr(D_2O): 0.88(t, CH_3); 1.30(sextet, $C\underline{H}_2CH_3$); 1.93(quintet, $C\underline{H}_2CH_2N^+$); 4.49(t, CH_2-N^+); 7.83(m, H-γ); 8.31(d, H-β); 8.34(s, H-α).

9c:

^{1}H-nmr($CDCl_3$): 0.85(t, CH_3); 1.3(m, $3CH_2$); 2.02(m, $C\underline{H}_2CH_2$-N^+); 4.68(t, CH_2-N^+); 7.86(m,H-γ); 8.55(d, H-β); 8.84(s, H-α).

9d:

^{1}H-nmr($CDCl_3$): 0.84(t, CH_3); 1.24(bs, $4CH_2$); 1.34(bs,$C\underline{H}_2CH_3$); 2.0(m, $C\underline{H}_2CH_2N^+$); 4.65(t, CH_2-N^+); 7.84(m, H-γ); 8.20(d, H-δ); 8.46(d, H-β); 8.92(s, H-α).

9e:

^{1}H-nmr($CDCl_3$): 0.85(t, CH_3); 1.23(bs, $6CH_2$); 1.25(bs, $C\underline{H}_2CH_3$); 2.0(m, $C\underline{H}_2CH_2$-N^+); 4.7(t, CH_2-N^+); 7.86(m, H-γ); 8.18(d,H-δ); 8.47(d, H-β); 8.92(s, H-α).

9f:

^{1}H-nmr($CDCl_3$): 0.86(t, CH_3); 1.22(bs, $8CH_2$); 1.32(m, $C\underline{H}_2CH_3$); 2.0(m,$C\underline{H}_2CH_2$-N^+); 4.64(t, CH_2-N^+); 7.82(m, H-γ); 8.15(d, H-δ); 8.42(d,H-β); 8.86(s, H-α).

4. N-Glucosyloxy Alkyl-3-dimethyl carbamoyl pyridinium

(scheme 4, **11**$a_{1,2}$;$b_{1,2}$)

Bromoalkyl glycosides were obtained through a glycosidation procedure similar to the one described for 5 . Quaternization between compounds **10**$a_{1,2}$;$b_{1,2}$ with 1 in conventional methods, was carried out and led to the formation of **11**$a_{1,2}$;$b_{1,2}$ (see scheme 4). These quaternised products were characterized by TLC and NMR .

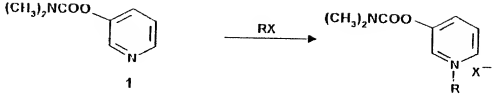
11a_1 (decyl):

^{1}H-nmr($CDCl_3$): 1.18(bs,6CH_2); 1.25(m, C$H_2$$CH_2$-O); 1.49(m, C$H_2$$CH_2$-$N^+$); 1.93,1.96,1.97,2.01 (4s, 4Ac); 2.98,3.11[2s, N-(CH_3)$_2$]; 2.98, 3.11(2s, N(CH_3)$_2$)3.39,3.64,3.79 (3m, C$H_a$$H_b$-0G); 3.95(t,H-5); 4.07(m,H-6_a); 4.2(dd, H-6_b), 4.42(d, H-β); 4.93(m, CH_2N^+,&H-2); 4.99(t, H-4); 5.13(t, H-3); 8.15(m, H-γ); 8.29(d, H-δ); 9.3(s,H-α); 9.44(d, H-β).

11a_2 (dodecyl):

^{1}H-nmr($CDCi_3$): 1.24 (bs, 8CH_2); 1.3 (m, 2CH_2); 1.59(m, CH_2); 2.0,2.03,2.05,2.09 (4S, 4Ac); 3.05,3.18 [2s, N-(CH_3)$_2$]; 3.47,3.7,3.87 (3m, C$H_a$$H_b$-OG); 4.04(t, H-5); 4.12(dd, H-6_a); 4.27(dd, H-6_b); 4.5(d, H-β); 5.0(m, CH_2-N^+,&H-2); 5.08 (t, H-4); 5.21(t,H-3); 8.17(m, H-γ); 8.33(d, H-δ); 9.32(s, H-α); 9.48(d, H-β).

Scheme 1



1

X: Br, I

2 a, b, c, d, e,.

a: R= C_4H_9

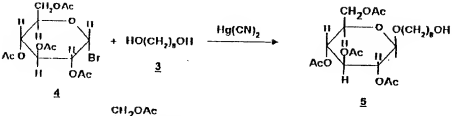
b: R= C_6H_{13}

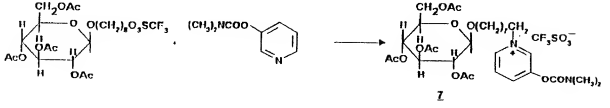
c: R= C_8H_{17}

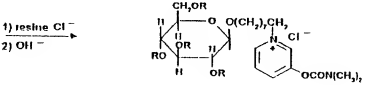
d: R= $C_{10}H_{21}$

e: R= $C_{12}H_{25}$

Scheme 2



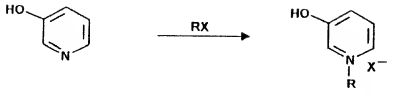




8 a, b

a: R= Ac b: R= H

Scheme 3



X: Br, I

9 a, b, c, d, e, f.

a: R= CH_3

b: R= C_4H_9

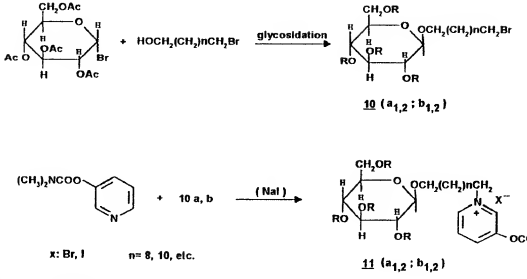
c: R= C_6H_{13}

d: R= C_8H_{17}

e: R= $C_{10}H_{21}$

f: R= $C_{12}H_{25}$

Scheme 4



Kinetics of AChE inhibition and reactivation in vitro

Carbamates such as pyridostigmine are potent inhibitors of AChE. The mode of AChE inhibition by carbamates is described by the following kinetic scheme:

$$E + I \underset{}{\overset{K_I}{\rightleftharpoons}} [E\text{-}I] \xrightarrow{k'} E_i \xrightarrow{k_s} E + I'$$

Where E, I, E-I, Ei and I' are the free enzyme, carbamate inhibitor, intermediate reversible complex formed between the enzyme and the carbamate, inhibited enzyme and dimethylcarbamoyl part of the carbamate molecule released spontaneously from the inhibited enzyme, respectively. The inhibition mechanism by carbamates includes the formation of a reversible complex E-I with dissociation constant K_I. The second step is the formation of a covalent

conjugate E_i between the dimethylcarbamoyl moiety of the PYR molecule and AChE, with a first order rate constant k'. Eventually, the inhibited enzyme (Ei) is reactivated spontaneously with a first order rate constant k_s. One can calculate the various kinetic rate constant by following the time-course of AChE inhibition and using the following two equations I and II (14):

I. The approach to steady state:

$$Ln[E_t/E_0 - E_t'/E_0(e/E)_{ss}) = (k'/(1+K_I/I) + k_s)t$$

II. The Steady state equation:

$$(e/E)_{ss} = (k_s/k' + k_s K_I/k')x1/I.$$

The bimolecular rate constant of inhibition k_i ($M^{-1}min^{-1}$) is calculated by k'/K_I. The inhibition kinetics was measured with purified fetal calf serum AChE using the Ellman method (21). The various kinetic parameters obtained for AChE inhibition by the various PYR derivatives are summarized in table 1. The values for K_I range between $1.2x10^{-7}$ and $2.3x10^{-5}$M . The spontaneous reactivation rate constant (k_s) obtained for all compounds range between 0.011-0.018 min^{-1}, indicating that the same dimethylcarbomoyl-AChE conjugate was formed upon inhibition by all PYR derivatives. The half-life time values derived from k_s values are 38-63 minutes as expected from spontaneous reactivation rate of dimethylcarbamoyl-AChE. The overall bimolecular rate constants range between $4.8x10^4$ - $2.9x10^6$ M^{-1} min^{-1}. These results are consistent with our prediction that the addition of a hydrocarbyl chain (with or without sugar residue) does not alter the intrinsic activity of the carbamate as an AChE inhibitor.

Table 1: Kinetic parameters of AChE inhibition by PYR derivatives

COMPOUND	K_I M	k' (min^{-1})	$t_{½}(k')$ (min)	k_s (min^{-1})	$t_{½}(k_s)$ (min)	k_i ($M^{-1}m^{-1}$)
PYRIDO	$5.0x10^{-7}$	0.15	5	0.016	43	$3.0x10^5$
PB	$8.8x10^{-6}$	1.12	0.62	0.012	58	$1.3x10^5$
PH	$2.9x10^{-6}$	0.14	5	0.016	43	$4.8x10^4$
PO	$1.8x10^{-5}$	1.61	0.43	0.014	49	$8.8x10^4$
POGA	$2.3x10^{-5}$	2.11	0.33	0.012	58	$9.2x10^4$
POG	$3.4x10^{-6}$	0.23	3.0	0.012	58	$1.5x10^4$
PD	$3.4x10^{-7}$	0.19	4	0.016	43	$5.6x10^5$
PDGA	$4.0x10^{-7}$	0.19	3.6	0.011	63	$4.7x10^5$
PDG	$8.7x10^{-7}$	0.09	7.7	0.006	110	$1.0x10^5$
PDOD	$2.0x10^{-6}$	0.89	0.78	0.016	43	$4.5x10^5$
PDOGA	$3.6x10^{-7}$	0.69	1	0.018	38	$1.9x10^6$
PDOG	$1.2x10^{-7}$	0.31	2.2	0.059	12	$2.6x10^6$

Acute Toxicity

The acute toxicity of the new compounds was determined by i.m. injection in mice and for some of the compounds by s.c. administration in rats. LD_{50} values were calculated according to the Spearman-Kerber method (15). The LD_{50} values obtained in mice for the various PYR-derivatives and their corresponding 3-hydroxy N-alkylpyridinium bromide derivatives are summarized in tables 2 and 3, respectively. Three compounds, PO, PD and POGA display significantly lower toxicity than PYR i.e. 37.6, 36.6, 33.9, respectively, as compared to 2.13 mg/kg (i.m.) obtained for PYR. The LD_{50} values obtained for PO, POGA and PD are 17.6, 16 and 17.2 fold higher than those obtained for PYR, respectively. The subcutaneous LD_{50} obtained for PO in rats (see footnote of table 2) 234.8 mg/kg is 47 fold larger than that for PYR, 5.15 mg/kg. It is pertinent to note that these three compounds are efficacious inhibitors of AChE with rate constants which are comparable to those of PYR (table 1). However, their in vivo toxicity is significantly lower than that of all other carbamate derivatives (table 2). The relative low toxicity indicates that these compounds are excellent candidates as potential drugs for various cholinergic inpairment diseases. Following carbamylation of AChE by all PYR derivatives there is a stoichiometric release of the 3-hydroxy N-hydrocarbyl pyridinium moiety. Since these leaving groups are putative metabolites of their parent compounds in vivo, we have synthesized these compounds and determined their acute toxicity and inhibitory potency with AChE. The 3-hydroxyalkylpyridinium compounds (the leaving groups) are far less toxic than their parent 3-carbamoyl compounds with LD_{50} values ranging at 600-1000 mg/kg (table 3). The leaving groups could inhibit AChE only at milimolar levels (not shown). The compounds PO, POGA and PD were chosen for further pharmacological studies due to their relative low toxicity.

Table 2: Acute toxicity of PYR derivatives

COMPOUND	LD50 (mice i.m.) mg/kg
PYRIDO *	2.13 (1.9-2.3)
PB	1.74 (0.96-3.2)
PII	6.51 (5.8-7.3)
PO **	37.58 (26.6-52.6)
POGA	33.86 (26.5-43.2)
POG	2.50 (1.7-3.7)
PD	36.59 (25.5-52.5)
PDGA	1.63 (0.74-3.56)
PDG	2.14 (1.9-2.4)
PDOD	1.34 (0.89-2.0)
PDOGA	1.19 (0.85-1.67)

* LD_{50} rat s.c. mg/kg 5.15 (4 - 6.6)
** LD_{50} rat s.c. mg/kg 234.8 (139.7 - 394.4)

Table 3: Acute toxicity of 3-hydroxy N-alkylpyridinium bromide compounds in mice

3-hydroxypyridinium derivatives 	LD_{50} (i.m., mg/kg)
R= Methyl	>1000
R= Butyl	>1000
R= Hexyl	507 (326 - 788)
R= Octyl	421 (299 - 591)
R= Decyl	923 (802 - 1063)
R= Dodecyl	>1000

Pharmacokinetics

One of the disadvantages of existing carbamates such as PYR and PHY is their short duration of action. PYR-derivatives containing either carbohydryl chains or various sugar moieties coupled to PYR via lipophilic carbohydryl chains display longer duration of action.PO and PD injected into rats caused a dose-dependent inhibition of whole blood ChE activity that was sustained at 17-47% inhibition level even after 24 hours (Table 4). Data from the literature show that the time-course of PYR elimination from blood is significantly shorter with a half-life of 1.2-1.8 hours following i.v. injection (16).

Table 4: Time -course of blood ChE inhibition in rats following s.c. administration of PO and PD

TIME (hr.)	% AChE Activity					
	PO (mg/kg)			PD (mg/kg)		
	10	20	40	10	20	40
0	100	100	100	100	100	100
0.25	81	51	-	76	75	68
0.5	83	56	63	62	74	64
1	53	67	63	62	65	55
1.5	88	67		100	75	93
2	67	67	63	81	55	82
2.5	74	59	73	-	-	-
3	72	76	58	-	-	-
4	76	58	-	83	72	100
5	-	58	-	-	-	-
6	-	53	-	86	65	82
24	83	67	-	53	70	69

Distribution in n-octanol/water as a test for lipophilicity

The permeability of small molecules (up to molecular weight of 1000 dalton) through the BBB is well correlated with their lipophilicity (17). As an indication for the lipophilicity of the compounds we have measured the distribution coefficients of some of the PYR-derivatives in n-octanol and aqueous solution. Concentrations of compounds in both phases was determined by the optical density (OD) at 266 - 272 nm. Calibration curve was performed with PYR in phosphate buffer saline (PBS) pH 7.4, at the range of 0125-25mM. 5ml of PYR solution or PYR-derivative solution in PBS were thoroughly mixed with 5ml n-octanol. Separation was observed following 1 minute centrifugation and the aqueous phase was separated from the organic phase. The absorbence spectrum of each phase was scanned at UV between 240-310nm. The peak value for each compound was used for the determination of its concentration according to the calibration curve obtained with PYR. The distribution coefficients are defined as the concentration ratio in n-octanol/PBS. The same distribution coefficients were obtained for at least two concentrations of PYR-derivatives which differed by two order of magnitude.(0.25-25mM). The distribution coefficients (k) of the tested compounds are summarized in table 5.

Table 5: Distribution coefficients (k) of PYR-derivatives

Compound	k (n-octanol/PBS)
PYR	0.009
PB	0.021
PH	0.149
POGA	0.275
PO	1.680
PD	10.816
PDOD	97.250

As can be seen from the k values in Table 5, PYR is not soluble in n-octanol whereas dodecyl-PYR (PDOD) is virtually soluble only in n-octanol. Progressive elongation of the alkyl chain attached to the quaternary pyridinium nitrogen increases the lipophilicity of the resulting derivative. These results indicate that the derivatives PH, PO, PD and PDOD are quite permeable through the BBB. The dual solubility of PH, PO and POGA in water and in n-octanol (table 5) is beneficial for transport of the drug from the periphery to the CNS on one hand and for the permeability through the BBB on the other hand. Addition of acetylated glucosyl moiety to the PYR-alkyl derivatives (POGA) reduced lipophilicity of PO from 1.680 to 0.275. However, the k value obtained for POGA lies between the k values of PH and PO indicating higher BBB permeability than PH. These results indicate that compounds which contain an alkyl chain longer or equal to hexyl are good candidates as centrally active drugs. The tendency to increase lipophylicity with elongation of the chain indicate that a PYR derivative in which the sugar is conjugated via decyl or dodecyl groups permeates the BBB and is more available to the CNS.

Compounds that contain functional groups such as glycosides seem to be bifunctional in terms of their mechanism of permeability into the brain, i.e. utilizing their lipophilicity as well as their endogenous membrane transporter to cross membranal barriers.

Analgesia in mice

One indication for BBB permeability is central activity of the PYR derivatives. It has previously been shown that analgesia may be induced by cholinomimetics, provided that they penetrate through the BBB. PHY, for example, is a potent analgetic (18) but PYR does not induce general analgesia, probably due to its quaternary nature. We found that the PYR-derivatives PO and PD which are soluble in n-octanol induce analgesia in three different tests in mice - hot plate, tail flip and tail clip (18). All three tests were carried out using male albino CHR mice weighing 25 ± 4 grams. For the hot plate test mice were injected with the tested drug (i.m) or with saline as a control and 15-20 min after the injection were placed on a hot plate (59°C) and the time required for the first response (leg lifting) were measured and recorded as response latency. For the tail clip mice were injected with drugs or saline as described above and 15-20 min later a paper clip was connected to the tail and time for first response (attempt to remove the clip) was measured and recorded as response latency. In the tail flip test, injections were similar to those described above and the mouse was inserted into 50 ml conic centrifuge tube and the tail left out. The tail was inserted into a water bath warmed to 59°C and the time for flipping the tail to avoid the hot water was measured and recorded as response latency. The mean response latencies obtained for PHY, (0.25 mg/kg) PYR (1.5 mg/kg) and two PYR-derivatives: PO and PD (both 8 mg/kg) are given in Table 6. As shown in table 6, PO and PD were active in all three tests indicating their central analgesic effect.

Table 6: Analgesic Effect of Carbamates

	Mean Response Latency (sec± sem)		
Compound	Hot plate	Tail clip	Tail flick
Control (saline)	6±1	5±2	2.5±1
Physostigmine	22	26±5	15±7
Pyridostigmine	6±3	14±6	4±2
PO	18	20	12
PD	ND*	20	14

* ND = not determined

Reversal of scopolamine-induced cognitive impairment in rats

Pharmacological manipulation of the central cholinergic system can provide significant changes in performance and behavior. Scopolamine, a centrally active antimuscarinic drug induces a profound decrement in learning and memory (19). Anticholinesterases can reverse this impairment, provided that they are accessible to the CNS (19). We have tested the efficacy of PYR-derivative PO to reverse scopolamine-induced impairment of acquisition in the passive avoidance behavioral task (20). Rats (Whistar male weighing 225-275 g) were injected subcutaneously with PYR-derivative (PO) or saline and 60 min later animals were injected sc with 0.3 mg/kg scopolamine. Fifteen minutes following the last injection animals were placed in the illuminated compartment of a standard shuttle cage. The latency to enter the dark compartment of the shuttle cage was measured following 3 minutes of acclimatisation period. Once the animal entered the dark compartment an electrical foot shock was delivered through a metal grid floor. The time required for the rats to cross to the dark compartment was recorded as the initial latency. Twentyfour hours later, the

rats were tested again for the latency to enter the dark compartment. A cutoff of 600 seconds was employed. The time required for entering the dark unsafe compartment was recorded as the 24 hours retention latency. Four groups of 10 rats each were employed in this study as follows: 1) Saline-saline (SA/SA); 2) Saline-Scopolamine-(SA/SC); 3) PO-Saline-(PO/SA); 4) PO-Scopolamine-(PO/SC). Parametric data are expressed as means ± SD and the significance of the differences among the groups were analyzed using the Mann-Whitney-U-test. Differences between groups were considered significant at $p<0.05$. Table 7 summarizes the means of the initial and the retention latencies obtained for these four test groups at three different doses of PO: 15, 20 and 25 mg/kg. The difference between the tested groups was analyzed according to the Mann-Whitney-U-test and presented in table 8. These results clearly demonstrate that PO at 15 and 20 mg/kg could reverse the effect of scopolamine in the passive avoidance test (see SA/SC vs. PO/SC, table 7 and 8). In addition, these results indicate that PO penetrate through the BBB as indeed expected from its distribution coefficient in n-octanol/water. PO at the dose of 25 mg also reversed the decremental effect by scopolamine, but at this dose certain toxic symptoms were observed (see PO-SA versus SA-SA, table 7 and 8).

Table 7: Retention latency of rats in the passive avoidance test - mean time for n=10 per group measured 24 hours post treatment with PO and scopolamine (SC) and initial test

DOSE mg/kg	Time (sec)	SA,SA	SA,SC	PO,SA	PO,SC
10	MEAN S.D.	570 79	93 83	486 137	249 183
15	MEAN S.D.	570 79	93 83	491 169	344 236
20	MEAN S.D.	570 79	93 83	600 0	253 190
25	MEAN S.D.	570 79	93 83	381 155	102 107

Table 8: Statistical Mann - Whitney - U - test for the retention latency data presented in table 7

DOSE (mg/kg)	PO,SA/ SA,SA	PO,SA/ SA,SC	PO,SA/ PO,SC	PO,SC/ SA,SC	PO,SC/ SA,SA
10	-	$p<0.002$	$p<0.02$	$p<0.1$	$p<0.002$
15	-	$p<0.02$	-	$p<0.05$	-
20	-	$p<0.05$	$p<0.05$	$p<0.02$	$p<0.02$
25	$p<0.05$	$p<0.002$	$p<0.002$	-	$p<0.002$

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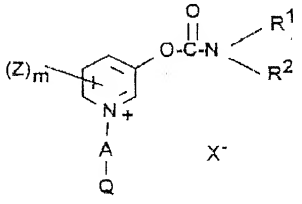
Au 1 24

CLAIMS:

1. A 3-position substituted pyridinium derivative of the general formula



where R^1 is -H, lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

R^2 is lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

A is an alkylene, alkenylene, alkynylene group spacer, and

Z designates dialkylcarbamoyl or lower alkyl and m is zero or 1.

Q is a sugar and phosphoryl-sugar group transporter recognition moiety adapted to enhance the transport of polar compounds via the blood brain barrier, through cell membranes, through kidney tubuli and through the gastrointestinal wall, which Q entity can optionally be substituted or coupled to a physiologically active acceptable moiety, and where X⁻ is an anion, where the Q transporter recognition moiety is selected from the following:

aldoses which include aldohexoses, ketoses which include ketohexoses, 6-deoxy hexoses, alditols, cyclohexitols, ascorbic acid and its derivatives, disacharides, oligosacharides which contain either sialic acid or not, amino sugars, phosphorylated sugars and polysacharides.

2. A compound according to claim 1 where A is $(CH_2)_n$, where n is from 4 to 24

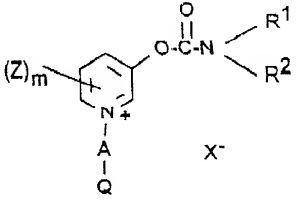
3. A pyridinium derivative according to claims 1or 2, where the sugar is an aldose that is selected from: glucose, mannose, galactose, aldopentoses,

AMENDED SHEET

aldotetroses and glyceroses and their corresponding aldonic and uronic acids.

4. A pyridinium derivative according to claim 3, where the sugar is a ketose that is selected from: fructose, sorbose and pentaketoses, where the deoxy hexose is fucose, mannitol, or mannose, where the alditol is selected from mannitol and dulcitol (C6), rebitol (C5), erythritol (C4), and glycerol (C3), where the cyclohexitol is selected from inositol and myoinositol, where the disaccharide is selected from lactose, maltose and sucrose, where the oligosaccharide contains sialic acid, or this is absent, where the amino sugar is selected from glucoseamine and N-acetylglucoseamine, where the phosphorylated sugar is phosphatidylinositol and where the polysaccharide is selected from cellulose and amylose which results in a sustained release drug form, where the polysacharides can either be covalently coupled to the PYR- hydrocarbyl moiety or by physical interaction such as ion-coupling or coating.

5. Pharmaceutical composition containing an effective quantity of a compound of the formula:



where R^1 is -H, lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl or cycloalkylalkyl,

AMENDED SHEET

Qu+84

R^2 is lower alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

A is an alkylene, alkenylene or alkynylene group spacer, and

Z designates dialkylcarbamoyl or lower alkyl and m is zero or 1.

Q is -H or a transporter recognition moiety adapted to enhance the transport of congeners via biological membranes, which Q entity can optionally be substituted or coupled to a physiologically active acceptable moiety, and where X^- is an anion.

6. A composition according to claim 5 where A is a hydrocarbyl group $(CH_2)_n$ where n is 1 to 24.

7. A composition according to claim 6 where n is 4 to 12.

8. A pharmaceutical composition of any of claims 5 to 7 for the treatment of. and for the alleviation of symptoms of CNS diseases associated with cholinergic disorders and for the alleviation of side-effects induced by antimuscarinic tricyclic antidepressants which comprise an effective quantity of a compound claimed in any of claims 1 to 4 or as defined in claim 5.

9. A composition according to anyy of claims 5 to 7, for the treatment of Alzheimer disease, tardive diskinesia, effects of stroke, neuralgic pains and general analgesic effect.

10. A composition according to any of claims 5 to 7 for the treatment of, and alleviation of symptoms of peripheral cholinergic disorders, glaucoma, myasthenia gravis, treatment of urine bladder dome (neurgenic urine bladder) and for the pretreatment of organophosphorus intoxication in combination with known antimuscarinic, antinicotinic drugs and antagonists of the excitatory amino acid receptors such as glutamate receptor, comprising an effective quantity of a compound claimed in any of claims 1 to 4 or as defined in claim 5.

11. A pharmaceutical composition according to any of claims 5 to 7 of prolonged action, for afflictions in the CNS and periphery, where the

pyridinium moiety is coupled to a suitable alkyl chain, a polysaccharide or an oligosaccharide residue.

12. A pharmaceutical composition according to claim 11 wherein the pyridinium moiety is coupled to a biodegradable polysaccharide for the slow release of the active component and for use in a biodegradable device for the sustained delivery of carbamates to the peripheral and central nervous system.

13. Pharmaceutical compositions according to claim 5 where 3-positioned substituted pyridinium compounds are combined with nicotinic and/or muscarinic agonists which confer higher eficacy than each of them by itself for treating cholinergic deficiency diseases.

14. Pharmaceutical combinations of the 3-positioned substituted pyridinium compounds as defined in claim 5 and compositions containing them as defined in claim 10 together with nicotinic and/or muscarinic and/or glutamate antagonists which confer higher efficacy than each one of them by itself, for the treatment of hypercholinergic impairments such as intoxication caused by reversible and irreversible cholinesterase inhibitors that are chemical warfare nerve agents.

.--ABSTRACT OF THE DISCLOSURE

A series of carbamates based on the structure of pyridostigmine (PYR) were synthesized and evaluated as potential drugs for the treatment of cognitive impairments associated with cholinergic perturbance such as in Alzheimer's disease. These compounds were examined for their cholinesterase inhibition, pharmacokinetics, acute toxicity, lipophilicity, reversal of scopolamine induced memory impairment in rats (passive avoidance) and analgesia in mice. These compounds include N-alkyl-PYR and various sugar-N-alkyl-PYR conjugates, being 3-position substituted pyridinium derivatives of general formula (I). Some of the new compounds are less toxic than PYR in rats and may serve for the treatment of other CNS-related diseases such as stroke and PNS-diseases such as: myasthenia gravis, glaucoma, neurogenic urinary bladder, neuralgic pains and as a pretreatment of organophosphorus intoxication.--

UTILITY PATENT
OR DESIGN
SOLE OR JOINT

EVENSON, MCKEOWN, EDWARDS & LENAHAN, P.L.L.C.
UNITED STATES LETTERS PATENT
DECLARATION AND POWER OF ATTORNEY

ATTORNEY'S DOCKET NO.
3102/44128

As a below named inventor, I declare that I believe I am the original, first and sole inventor (if only one name is listed at Item 201 below, or a joint inventor if plural) named are listed below at Items 201 et. seq. of subject matter which is claimed and for which a patent is sought for the invention entitled:

PYRIDINIUM DERIVATIVES AND PHARMACEUTICAL-COMPOSITIONS CONTAINING THEM

which is described and claimed in:

101 [ ] the attached specification (a) the specification in application Serial No. 09/029,543 filed 02/26/98
(for declaration not accompanying application papers)

and (if applicable) amended on

102 [x] International (PCT) application No. PCT/IL96/00089 filed 08/29/96 and as amended on (if any)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known by me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit, under Title 35, United States Code, §119, of any foreign application(s) for patent or inventor's certificate listed in Item 103 below and have also identified in Item 103 below any foreign application(s) for patent or inventor's certificate having a filing date before that of the application for which priority is claimed.

I hereby claim the benefit, under Title 35, United States Code, §120, of any U.S. application(s) listed in Item 105 below, if the application is a continuation-in-part, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior U.S. application(s) identified in Item 105 below and the national or PCT international filing date of this application.

FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 (6 for Design) MONTHS PRIOR TO THE FILING DATE OF THIS APPLICATION THE PRIORITY OF WHICH WHERE PERMITTED IS HEREBY CLAIMED UNDER 35 U.S.C. §119

	COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED YES	PRIORITY CLAIMED NO
103	ISRAEL	115118	31/8/95	X	

105	THIS APPLICATION IS A: [ ] CONTINUATION [ ] DIVISION [ ] CONTINUATION-IN-PART OF PRIOR U.S. APPLICATION	SERIAL NO.	FILED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

JAMES F. MCKEOWN Registration No. 25,406
HERBERT I. CANTOR Registration No. 24,392
DONALD D. EVENSON Registration No. 26,160
JOSEPH D. EVANS Registration No. 26,269
GARY R. EDWARDS Registration No. 31,824
JEFFREY D. SANOK Registration No. 32,169

SEND CORRESPONDENCE TO: EVENSON, MCKEOWN, EDWARDS & LENAHAN, P.L.L.C. Suite 700 1200 G Street, N.W. Washington, D.C. 20005

DIRECT TELEPHONE CALLS TO: 202-628-8800

Suite 700 1200 G St. DC 20005-3814 (202)-628-8800
NW Washington DC 20005-3814

Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME OF INVENTOR	LAST NAME RACHAMAN	FIRST NAME Eliezer	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 8/A Hertzog, 76182 Rehovot, Israel		
202	FULL NAME OF INVENTOR	LAST NAME HELDMAN	FIRST NAME Eliahu	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 8 Simtat Hamuchtar,76503 Rehovot, Israel		
203	FULL NAME OF INVENTOR	LAST NAME ADANI	FIRST NAME Rachel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Moshav Gealia	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 76885 Moshav Gealia, Israel		
204	FULL NAME OF INVENTOR	LAST NAME AMITAI	FIRST NAME Gabriel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 36 Sirani Street, 76229 Rehovot, Israel		
205	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION	STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS		
206	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION	STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS		

[ ] Seventh (and more) coinventors on page 3

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issued thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE	DATE	DATE
SIGNATURE OF INVENTOR 204 Gabi Amitai	SIGNATURE OF INVENTOR 205	SIGNATURE OF INVENTOR 206
DATE Dec 3, 1998	DATE	DATE

UTILITY PATENT
OR DESIGN
SOLE OR JOINT

EVENSON, McKEOWN, EDWARDS & LENAHAN, P.L.L.C.
UNITED STATES LETTERS PATENT
DECLARATION AND POWER OF ATTORNEY

ATTORNEY'S DOCKET NO.
3102/44138

As a below named inventor, I declare that I believe I am the original, first and sole inventor if only one name is listed at item 201 below, or a joint inventor if plural names are listed below at items 201 et. seq. of subject matter which is claimed and for which a patent is sought for the invention entitled:

PYRIDINIUM DERIVATIVES AND PHARMACEUTICAL-COMPOSITIONS CONTAINING THEM

which is described and claimed in:

191 [ ] the attached specification (a) the specification in application Serial No. 08/629,543 filed 02/28/96
(for declaration not accompanying application papers)

and (if applicable) amended on

192 [x] International (PCT) application No. PCT/IL95/00089 filed 08/23/95 and as amended on (if any)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known by me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56. I hereby claim the benefit or priority, under Title 35, United States Code, §119, of any foreign application(s) for patent or inventor's certificate listed in item 193 below and have also identified in item 193 below any foreign application(s) for patent or inventor's certificate having a filing date before that of the application for which priority is claimed.

I hereby claim the benefit, under Title 35, United States Code, §120, of any U.S. application(s) listed in item 195 below. If this application is a continuation-in-part, I/we/he/she the subject matter of any of the claims thereof is not disclosed in the prior U.S. application(s) identified in item 195 below in the manner provided by the first paragraph of Title 35, United States Code, §112. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior U.S. application(s) identified in item 195 below and the national or PCT international filing date of this application.

FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 (6 If a Design) MONTHS PRIOR TO THE FILING DATE OF THIS APPLICATION THE PRIORITY OF WHICH WHERE PERMITTED IS HEREBY CLAIMED UNDER 35 U.S.C. §119

	COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED YES	PRIORITY CLAIMED NO
193	ISRAEL	115113	31/8/95	X	

195	THIS APPLICATION IS A: [ ] CONTINUATION [ ] DIVISION [ ] CONTINUATION-IN-PART OF PRIOR U.S. APPLICATION	SERIAL NO.	FILED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

JAMES F. McKEOWN Registration No. 25,406	HERBERT I. CANTOR Registration No. 24,392	DONALD D. EVENSON Registration No. 26,160
JOSEPH D. EVANS Registration No. 26,269	GARY R. EDWARDS Registration No. 31,824	JEFFREY D. SANOK Registration No. 32,169

200 CORRESPONDENCE TO:	EVENSON, McKEOWN, EDWARDS & LENAHAN, P.L.L.C. Suite 700 1200 G Street, N.W. Washington, D.C. 20005	DIRECT TELEPHONE CALLS TO: 202-628-8800

Suite 700 1200 G St. DC 20005-3814 (202)-628-8800
1200 G Street, N.W. Washington DC 20005-3814

Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME OF INVENTOR	LAST NAME RACHAMAN	FIRST NAME Eliezer	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 8/A Herzeg, 76182 Rehovot, Israel		
202	FULL NAME OF INVENTOR	LAST NAME HELDMAN	FIRST NAME Eliahu	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 8 Simtat Hamuchtar,76603 Rehovot, Israel		
203	FULL NAME OF INVENTOR	LAST NAME ADANI	FIRST NAME Rachel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Moshav Gealig	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 76865 Moshav Gealia, Israel		

204	FULL NAME OF INVENTOR	LAST NAME AMITAI	FIRST NAME Gabriel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 36 Sirani Street, 76229 Rehovot, Israel		
205	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION	STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS		
206	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION	STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS		

[ ] Several (and more) continuation on page 8

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issue thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203 Rellie Adani ×
DATE	DATE	DATE Dec. 3, 1998
SIGNATURE OF INVENTOR 204	SIGNATURE OF INVENTOR 205	SIGNATURE OF INVENTOR 206
DATE	DATE	DATE

UTILITY PATENT
OR DESIGN
SOLE OR JOINT

EVENSON, McKEOWN, EDWARDS & LENAHAN, P.L.L.C.
UNITED STATES LETTERS PATENT
DECLARATION AND POWER OF ATTORNEY

ATTORNEY'S DOCKET NO.
3103/44198

As a below named inventor, I declare that I believe I am the original, first and sole inventor if only one name is listed at item 201 below, or a joint inventor if plural names are listed below at items 201 et. seq. of subject matter which is claimed and for which a patent is sought for the invention entitled:

PYRIDINIUM DERIVATIVES AND PHARMACEUTICAL-COMPOSITIONS CONTAINING THEM

which is described and claimed in:

101 [ ] the attached specification [a] the specification in application Serial No. 08/629,543 filed 02/28/98
(for declaration not accompanying application papers)

and *(if applicable)* amended on

102 [x] International (PCT) application No. PCT/IL96/00089 filed 08/23/96 and as amended on (if any)

I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known by me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit of priority, under Title 35, United States Code, §119, of any foreign application(s) for patent or inventor's certificate listed in item 103 below and have also identified in item 103 below any foreign application(s) for patent or inventor's certificate having a filing date before that of the application for which priority is claimed.

I hereby claim the benefit, under Title 35, United States Code, §120, of any U.S. application(s) listed in item 104 below. If this application is a continuation-in-part, I acknowledge the duty of the claims thereof is not disclosed in the prior U.S. application(s) identified in item 104 below in the manner provided by the first paragraph of Title 35, United States Code, §112. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior U.S. application(s) identified in item 104 below and the national or PCT international filing date of this application.

FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 (6 if a Design) MONTHS PRIOR TO THE FILING DATE OF THE APPLICATION THE PRIORITY OF WHICH WHERE PERMITTED IS HEREBY CLAIMED UNDER 35 U.S.C. §119

	COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED YES	PRIORITY CLAIMED NO
103	ISRAEL	115113	31/8/95	X	

104	THIS APPLICATION IS A: [ ] CONTINUATION [ ] DIVISION [ ] CONTINUATION-IN-PART OF PRIOR U.S. APPLICATION	SERIAL NO.	FILED	

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

JAMES F. McKEOWN Registration No. 25,406	HERBERT I. CANTOR Registration No. 24,392	DONALD D. EVENSON Registration No. 26,160
JOSEPH D. EVANS Registration No. 30,269	GARY R. EDWARDS Registration No. 31,824	JEFFREY D. SANOK Registration No. 32,169

SEND CORRESPONDENCE TO:	EVENSON, McKEOWN, EDWARDS & LENAHAN P.L.L.C. Suite 700 1200 G Street, N.W. Washington, D.C. 20005	DIRECT TELEPHONE CALLS TO: 202-628-8800

Suite 700 1200 G St. DC 20005-3814 (202)-628-8800
the Washington DC 20005-3814

Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME OF INVENTOR	LAST NAME RACHAMAN		FIRST NAME Eliezer	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot		STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 8/A Herzog, 76182 Rehovot, Israel			
202	FULL NAME OF INVENTOR	LAST NAME HELDMAN		FIRST NAME Eliahu	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot		STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 8 Simtat Hamuchtar,76503 Rehovot, Israel			
203	FULL NAME OF INVENTOR	LAST NAME ADANI		FIRST NAME Rachel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Moshav Gesila		STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 76886 Moshav Gesila, Israel			

204	FULL NAME OF INVENTOR	LAST NAME AMITAI		FIRST NAME Gabriel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot		STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 36 Sirani Street, 76229 Rehovot, Israel			
205	FULL NAME OF INVENTOR	LAST NAME		FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION		STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS			
206	FULL NAME OF INVENTOR	LAST NAME		FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION		STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS			

[ ] Seventh (and more) inventors on page 3

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issue thereon.

SIGNATURE OF INVENTOR 201 E. Rachaman	SIGNATURE OF INVENTOR 203	SIGNATURE OF INVENTOR 205
DATE Dec. 3, 1998	DATE	DATE
SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 204	SIGNATURE OF INVENTOR 206
DATE	DATE	DATE

EVENSON, MCKEOWN ... PHONE NO. : 2026288829

UTILITY PATENT
OR DESIGN
SOLE OR JOINT

EVENSON, MCKEOWN, EDWARDS & LENAHAN, P.L.L.C.
UNITED STATES LETTERS PATENT
DECLARATION AND POWER OF ATTORNEY

ATTORNEY'S DOCKET NO.
3103/44138

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	COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED YES	NO
103	ISRAEL	115113	31/8/95	X	

	THIS APPLICATION IS A:		SERIAL NO.	FILED
105	[ ] CONTINUATION [ ] DIVISION	[ ] CONTINUATION-IN-PART OF PRIOR U.S. APPLICATION		

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

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JOSEPH D. EVANS Registration No. 26,269	GARY R. EDWARDS Registration No. 31,824	JEFFREY D. SANOK Registration No. 32,169

SEND CORRESPONDENCE TO:	EVENSON, MCKEOWN, EDWARDS & LENAHAN, P.L.L.C. Suite 700 1200 G Street, N.W. Washington, D.C. 20005	DIRECT TELEPHONE CALLS TO: 202-628-8800

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NW Washington DC 20005 - 3814

RECEIVED TIMEDEC. 6. 9:44AM PRINT TIMEDEC. 6. 9:52AM

Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME OF INVENTOR	LAST NAME RACHAMAN 100	FIRST NAME Eliezer	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot ILK	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 9/A Hertzog, 76182 Rehovot, Israel		
202	FULL NAME OF INVENTOR	LAST NAME HELDMAN 200	FIRST NAME Eliahu	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot ILK	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 8 Simtat Hamuchtar,76503 Rehovot, Israel		
203	FULL NAME OF INVENTOR	LAST NAME ADANI 300	FIRST NAME Rachel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Moshav Gealia ILK	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 76885 Moshav Gealia, Israel		

204	FULL NAME OF INVENTOR	LAST NAME AMITAI 400	FIRST NAME Gabriel	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION Rehovot ILK	STATE OR COUNTRY Israel	CITIZENSHIP Israeli
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 36 Sireni Street, 76229 Rehovot, Israel		
205	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION	STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS		
206	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION	STATE OR COUNTRY	CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS		

[ ] Seventh (and more) coinventors on page 3

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SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202 Elliahu Heldman	SIGNATURE OF INVENTOR 203
DATE	DATE December 3, 1998	DATE
SIGNATURE OF INVENTOR 204	SIGNATURE OF INVENTOR 205	SIGNATURE OF INVENTOR 206
DATE	DATE	DATE

#5

Attorney Docket: 3103/44139
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: ELIEZER RACHAMAN ET AL.

Serial No.: 09/029,543 Group Art Unit:

Filed: FEBRUARY 26, 1998 Examiner:

Title: PYRIDINIUM DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

SUBSTITUTE POWER OF ATTORNEY UNDER 37 CFR.1.32

BOX PCT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

THE STATE OF ISRAEL, Prime Ministers Office Israel Institute for Biological Research, the assignee of the entire right, title and interest in and to the above-identified application, by virtue of an assignment dated December 3, 1998, and filed for recording on December 8, 1998, a copy of which is attached hereto, hereby elects to prosecute the application to the exclusion of the inventors pursuant to 37 CFR 1.32, and hereby appoints the following as its attorneys in this case to prosecute this application, to transact all business in the Patent and Trademark Office in connection therewith, and to receive the letters patent:

Martin Fleit, Reg. No. 16,900; Herbert I. Cantor, Reg. No. 24,392; James F. McKeown, Reg. No. 25,406; Donald D. Evenson, Reg. No. 26,160; Joseph D. Evans, Reg. No. 26,269; Gary R. Edwards, Reg. No. 31,824; and Jeffrey D. Sanok, Reg. No. 32,169.

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Serial No. 09/939,843

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Respectfully submitted,

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Deputy Managing Director
Title: for Finance

Date: 28/12/98